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# Influence of exercise on visceral pain: an explorative study in healthy volunteers

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**Background and objectives:** Contradictory results have been found about the effect of different exercise modalities on pain. The aim of this study was to investigate the early effects of aerobic and isometric exercise on different types of experimental pain, including visceral pain, compared to an active control condition.

**Methods:** Fifteen healthy subjects (6 women, mean [standard deviation] age 25 [6.5] years) completed 3 interventions consisting of 20 minutes of aerobic cycling, 12 minutes of isometric knee extension and a deep breathing procedure as active control. At baseline and after each intervention, psychophysical tests were performed, including electrical stimulation of the esophagus, pressure pain thresholds and the cold pressor test as a measure for conditioned pain modulation. Participants completed the Medical Outcome Study Short-Form 36 and State-Trait Anxiety Inventory prior to the experiments. Data were analyzed using two-way repeated measures analysis of variance.

**Results:** No significant differences were found for the psychophysical tests after the interventions, compared to baseline pain tests and the control condition.

**Conclusion:** No hypoalgesic effect of aerobic and isometric exercise was found. The evidence for exercise-induced hypoalgesia appears to be not as consistent as initially thought, and caution is recommended when interpreting the effects of exercise on pain.

**Keywords:** motor activity, breathing exercises, pain measurement, pain perception

## Abbreviations

ANOVA: analysis of variance, BP: blood pressure, CPM: conditioned pain modulation, EIH: exercise-induced hypoalgesia, HR: heart rate, MCS: mental component score, MOS SF-36: medical outcomes study short-form-36 health survey, PCS: physical component score, PPT: pressure pain threshold, STAI: State-Trait Anxiety Inventory, VAS: visual analogue scale,  $VO_{2max}$ : maximal oxygen uptake.

## Introduction

The modulatory effect of physical exercise on pain perception has been widely studied. Many studies found a favorable effect in healthy volunteers on somatic pain indicated with the term EIH, which is manifested as increased pain thresholds and pain tolerance levels and decreased evoked pain ratings during and immediately after exercise, persisting for 10–30 minutes post exercise.<sup>1</sup> This effect is seen with several types of exercise, including aerobic exercise,<sup>2–4</sup> isometric exercise<sup>5–10</sup> and dynamic resistance exercise.<sup>11,12</sup> EIH has been shown in healthy individuals, as well as in patients with chronic low back pain,<sup>13,14</sup> shoulder myalgia,<sup>15</sup> fibromyalgia<sup>16–18</sup> and chronic musculoskeletal pain,<sup>19</sup>

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although large variations were demonstrated between chronic pain syndromes.<sup>20</sup>

In a meta-analysis, Naugle et al<sup>1</sup> combined different experimental pain threshold effect sizes from several studies, which were averaged for each exercise type and pain testing method and adjusted for sample size. They calculated effect sizes using Cohen's *d* as a standardized mean difference between the control condition and the exercise condition and reported moderate effect size of 0.43 for aerobic exercise (4 studies), a large effect size of 1.05 for isometric exercise (9 studies) and 0.83 for dynamic resistance exercise (2 studies). Furthermore, the effect sizes for pain intensity ratings reported by the participants varied from 0.64 (7 studies) to 0.72 (7 studies) to 0.75 (2 studies) for the 3 exercise types, respectively.<sup>1</sup>

However, not all studies found positive effects. Some studies found the hypoalgesic effect only in women, not in men,<sup>4,5</sup> some found only trivial effects at lower exercise intensities and durations<sup>8,21,22</sup> and others used pain testing methods with more variability in the effect size such as thermal stimulation.<sup>23</sup>

This contradicting evidence from the literature is not surprising due to many methodological variations. Studies have used different types of exercise and different exercise intensities, durations and measures to control the intensity. Moreover, varying methods of pain testing were used, including pressure, electrical and thermal stimulation, which were applied to different body sites and yielded pain thresholds, suprathreshold intensity ratings or general pain intensity ratings.<sup>1</sup> Another method of pain testing used is CPM, the ability to influence the incoming pain signals from the periphery via descending pain inhibition from brainstem centers. It has been shown that CPM can induce a transient hypoalgesic effect, which involves a neural network comprising the nucleus tractus solitarius and brainstem nuclei.<sup>24–26</sup> The most frequently studied stimuli are cold water immersion as conditioning stimulus and PPTs as test stimulus, which have shown good inter- and intrasession reliability.<sup>27</sup> The dissimilarities between study methods make comparisons between studies and interpretations of the results difficult.

Another limitation in most study designs is the lack of a control condition. Only a few studies used quiet rest for this purpose,<sup>2,3,10</sup> which is not adequate, since it does not control for attention differences and cardiovascular changes during exercise. In this explorative study, a deep breathing procedure was used as active control to take into account the increased breathing rate and attention. Moreover, deep breathing controls for the increased HR in exercise conditions by causing an HR reduction through parasympathetic activation.

Furthermore, so far known, all studies evaluated the effect of exercise on somatic pain, thereby disregarding visceral pain as a common cause of chronic pain. Visceral pain is difficult to characterize in contrast to somatic pain, mainly due to diffuse termination of afferents and poor corticotropic organization.<sup>28</sup> This makes treatment often challenging for physicians and alternative treatments very relevant. To obtain detailed information about the visceral pain response, experimental pain models can be used to induce visceral pain in a controlled manner, while psychophysical and neurophysiological measures are carried out. In this explorative study, an experimental model of acute visceral pain was used, by delivering single pulse electrical stimuli in the esophagus. To measure the effect of exercise on other pain modalities than those of visceral origin, PPTs and CPM were also assessed. The hypothesis was that both aerobic and isometric exercise would induce hypoalgesia on experimentally induced pain, based on the psychophysical measurements. Hence, the aim of this study was to investigate the immediate effect of aerobic and isometric exercise compared with deep breathing as active control condition on visceral pain sensitivity, PPTs and induction of descending inhibition.

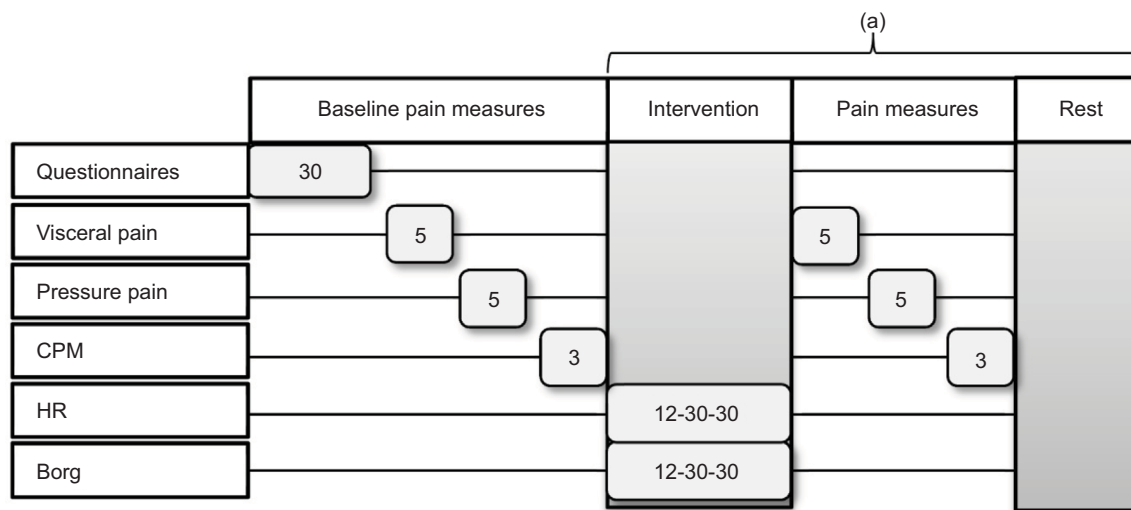
## Methods

### Participants

Fifteen participants (9 men and 6 women, mean [SD] age 25 [6.5] years) were recruited in Region North Jutland in Denmark. These healthy volunteers had no history of cardiovascular, gastrointestinal or neurological disorders that could interfere with the exercise interventions and pain measurements. The study protocol was approved by the Regional Ethics Committee of Northern Jutland, Denmark (N-200900), and all participants signed informed consent. Participants were instructed to refrain from any pain-modifying medication, alcohol and physical exercise 24 hours prior to the experimental procedure. Additionally, to minimize the unpleasantness of the esophageal tube, food, drinks, nicotine and caffeine were restrained 2 hours prior to insertion.

### Study design

The crossover study with a randomized order of interventions was carried out at Mech-Sense, Department of Gastroenterology at Aalborg University Hospital. An overview of study procedures can be seen in Figure 1. Baseline pain measurements were conducted, including esophageal electrical stimulation, pressure algometry and cold pressor test. Within 5 minutes thereafter, 3 interventions: aerobic



**Figure 1** Timeline study procedures.

**Notes:** Interventions consisted of aerobic cycling, isometric knee extension and deep breathing as active control condition, followed by the pain measures and 30 minutes of rest. The numbers indicate the time in minutes. <sup>(a)</sup>This block was repeated twice.

**Abbreviations:** CPM, conditioned pain modulation; HR, heart rate; Borg, Borg's Rate of Perceived Exertion scale.

bicycling exercise, isometric knee extensions and a control condition were randomly performed to avoid bias of period effects and order effects. The randomization list was generated from <http://www.randomisation.com>. Directly after every intervention, the pain measurements were repeated, followed by a resting period of 30 minutes.

## Questionnaires

The participants filled out the Danish MOS SF-36, a general health survey of 36 questions. It produces a profile of 8 scales, addressing several health aspects, and 2 composite summary scores of physical health (PCS) and mental health (MCS).<sup>29</sup> Furthermore, they filled out the Y1 and Y2 form of the Danish translation of STAI, which evaluates general emotional, cognitive and behavioral aspects of anxiety. The Y1 form was about anxiety "at this moment" and the Y2 form about anxiety "in general."<sup>30</sup>

## Visual analogue scale

A modified VAS comprising ratings of non-painful (1–5) and painful sensations (5–10) was used to rate the sensation of electrical stimulation in the esophagus. This scale was used as strong pain stimuli to the esophagus carry the risk of excessive vomiting, which makes it difficult to use a pure pain VAS. It has previously been used for more than 50 studies of the gastrointestinal tract, where it has shown to be robust and reliable.<sup>31,32</sup>

The following anchor words were used to further assist in rating on the scale. 1, vague perception of mild sensation;

2, definite perception of mild sensation; 3, vague perception of moderate sensation; 4, definite perception of moderate sensation; 5, pain detection threshold; 6, slight pain; 7, moderate pain; 8, medium pain intensity; 9, intense pain and 10, unbearable pain.

For the cold pressor test, a pure pain VAS was used, where "0" indicated no pain, "5" moderate pain and "10" the worst pain imaginable. For the pressure algometry, VAS scores were used to clarify at which VAS level participants indicated their PPT.

## Psychophysical tests

### Visceral pain sensitivity

For electrical stimulation of the esophagus, a 2.6 mm diameter probe was used with 2 bipolar platinum ring electrodes attached to it, at 8.0 and 9.0 cm from the distal end (Gaeltec transducer; Gaeltec Ltd., Isle of Skye, Scotland, UK). The probe was inserted through the mouth until the interelectrode space was positioned at 34 cm from the frontal teeth and taped to the skin. Before stimulation, the impedance was checked and kept <3 kΩ by giving some water or by changing the participants' position. During stimulations, a 3-lead electrocardiogram was recorded to monitor the heart. Single pulse electrical stimulation of 2 ms was provided by a computer-controlled current stimulator, which started at an intensity of 0 mA and was increased with steps of 0.5 mA, with a predefined maximum of 60 mA. The participants scored the sensation with the modified VAS, indicating when they reached 1, 3, 5 and 7 on the VAS. At a VAS score

corresponding to 7, corresponding to moderate pain, electrical stimulation was stopped.

### Pressure algometry

PPTs were measured using a hand held algometer with a standard probe tip of 1 cm<sup>2</sup> (SBMEDIC Electronics, Solna, Sweden). The algometer was pressed on 5 locations at the dominant site, namely on the medial part of the trapezius muscle, the dorsal T10 dermatome, the thenar muscle, the rectus femoris muscle and the abductor hallucis muscle as shown in Figure 2. Starting at 0 kPa, the pressure was gradually increased with 30 kPa/s. The participants were asked to indicate the moment the sensation changed from pressure to pain, whereupon pressure testing was stopped immediately and the maximal reached pressure was noted as PPT. The mean PPT of the 5 locations was calculated for

every participant in every intervention. All measurements were performed by the same investigator.

### Cold pressor test

CPM was examined with the cold pressor test, studying the ability of descending inhibitory modulation. The participant immersed their nondominant hand up to the wrist with the fingers spread in a water bath containing cold circulating water with a temperature of 2°C (±0.1°C). They kept the hand in the water for 2 minutes, or less if the pain was unbearable and reached the maximum VAS score of 10 on the pure pain VAS. Before and immediately after the test, the PPT on the quadriceps muscle at the nondominant site was examined. Furthermore, the participant rated the pain every 30 seconds during the test and immediately after, with the VAS.<sup>33</sup> The relative change between the PPT before and the PPT after the cold water test was calculated in percentages, as well as the mean VAS scores during the immersion.

## Interventions

### Aerobic bicycling exercise

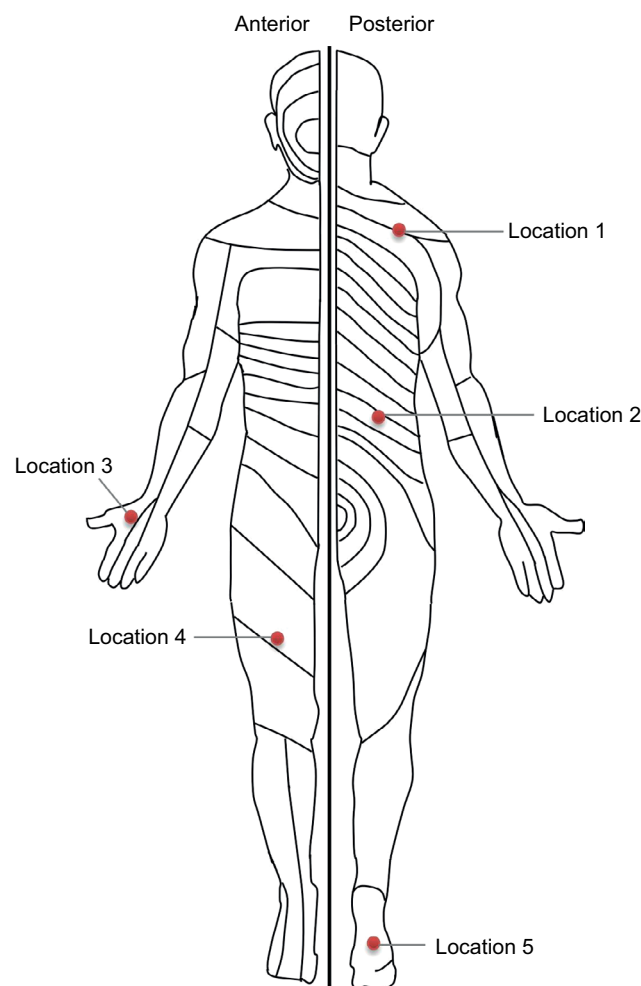
After warming up for 10 minutes at a self-selected cycling intensity, the participants bicycled 20 minutes at 75%–88% of their HR<sub>max</sub>, which corresponds to 60%–80% of their VO<sub>2max</sub>. The individual HR that matches this intensity was calculated with the Karvonen formula, which is related to the age-predicted HR<sub>max</sub> but allows for differences in resting HR: Target HR = [(220 – age – resting HR) × %Intensity] + resting HR.<sup>34</sup> The participants had visual feedback of the HR on the oximeter (Nellcor™ OxiMax N-65; Tyco Healthcare Group LP, Pleasanton, CA, USA) and were encouraged to keep their HR in the 75%–88% range by cycling faster or adjusting the resistance of the bicycle.

### Isometric knee extension

The participants performed isometric knee extension of the quadriceps muscle. They sat straight with 90° flexion in the hip joint and in 0° extension in the knee joint. A weight strap of 0.75 kg was attached around the ankle at the dominant side, to obtain the same strenuous intensity in all participants. They were instructed to extend the knee, without lifting the upper leg from the bed, for a maximum of 12 minutes or to exhaustion.

### Control condition

Deep breathing was used as active control condition. The participants executed a deep breathing procedure for 30 minutes, consisting of 10 rounds. For 1 minute in every round, the participants inhaled quickly applying diaphragmatic



**Figure 2** Locations pressure algometry.

**Note:** Pressure algometry locations, including the trapezius muscle (location 1), T10 dermatome (location 2), thenar muscle (location 3), rectus femoris muscle (location 4) and abductor hallucis muscle (location 5).

(abdominal) breathing and hold their breath for a total of 4 seconds. Then, they exhaled to their forced expiratory vital capacity for 6 seconds, through pursed lips. This produces breathing at a frequency of 0.1 Hz, corresponding to 6 breaths per minute. After this minute, there was a period with normal breathing until the HR and breathing had normalized and the participant was ready for the next round.<sup>35</sup>

## Exercise measurements

### HR

To measure the cardiovascular reaction on exercise, HR was measured before and every 5 minutes during the isometric knee extension. In the aerobic cycling exercise, HR was measured every 5 minutes. In the deep breathing intervention, HR measurements were used to monitor the parasympathetic nervous system activation, indicated by a decrease in HR. To demonstrate a vagal activation, the starting and lowest HR in every round of deep breathing were noted.

### Borg

The Borg's Rate of Perceived Exertion scale ranges from 6 to 20 to follow the general HR of a healthy adult by multiplying with 10. In this scale, "6" means no exertion at all and "20" means maximal exertion. The participants were told to focus on the overall feeling of exertion and not just to 1 factor, such as muscle pain. The score was asked every 5 minutes during aerobic cycling exercise and every 2.5 minutes during isometric knee extension. The Borg scale was not used in the control condition, as exertion was not applicable to this intervention.

## Statistics

The absolute outcomes and baseline-corrected outcomes (baseline values subtracted from the pain measurements) were compared between the interventions and control condition using two-way RM-ANOVA. For the visceral stimulation, the factors intervention (3 levels) and VAS score (4 levels) were analyzed, for the pressure algometry, the factors intervention (3 levels) and location (5 levels). If an overall difference was found, post hoc analyses (Student's *t*-test compared with Bonferroni corrected *p*-values) were used to describe the differences within the pain measurements. One-way ANOVA was used to compare the differences between interventions (3 levels) regarding the change in pain thresholds before and after the cold pressor test. *p*-values <0.05 were considered significant. In this explorative study, effect sizes were calculated using Cohen's *d*, which is a standardized mean difference. The

effect sizes were calculated with the use of the baseline-corrected data, as the mean for the deep breathing condition minus the mean for the 2 exercise interventions, divided by the pooled standard deviation. It was calculated for the visceral pain sensitivity at moderate pain (VAS 7), the mean PPT from pressure algometry and the mean relative increase in PPT after CPM.

## Results

### Baseline characteristics and questionnaires

The baseline characteristics of the study participants are presented in Table 1.

### Psychophysical tests

The data are presented as mean (SD) in the text and in Table 2.

### Visceral pain sensitivity

There was no significant difference between the baseline-corrected mean (SD) of the control condition and the exercise interventions for the esophageal stimulation ( $F(2, 78)=2.0$ ;  $p=0.15$ ), as shown in Figure 3. The effect size at moderate visceral pain for aerobic cycling was  $d=-0.39$  and for the isometric exercise  $d=-0.18$ . These results indicate that exercise induced no visceral hypoalgesia.

### Pressure algometry

When comparing the baseline-corrected means of the PPTs on the 5 locations as shown in Figure 4, no significant difference was found between the control condition and the exercise interventions ( $F(2, 112)=0.37$ ;  $p=0.7$ ). The effect size for aerobic cycling was  $d=-0.09$  and for isometric exercise  $d=-0.06$ . These data suggest that no hypoalgesia was induced by exercise.

**Table 1** Baseline characteristics of the healthy volunteers (n=15)

Characteristics	Mean (SD)
Age, years	25 (6.5)
Gender, M:F	9:6
Height, m	1.79 (0.08)
Weight, kg	73 (9.7)
Body mass index, kg/m <sup>2</sup>	22.6 (2.0)
STAI Y1 score <sup>a</sup>	27.67 (5.5)
STAI Y2 score <sup>a</sup>	31.20 (9.7)
MOS SF-36 PCS	54.02 (3.4)
MOS SF-36 MCS	51.93 (5.0)

**Note:** <sup>a</sup>Y1: state, score at this moment; Y2: trait, score in general.

**Abbreviations:** M, male; F, female; STAI, State-Trait Anxiety Inventory; MOS SF-36, Medical Outcome Short-Form 36; PCS, physical component summary; MCS, mental component summary.

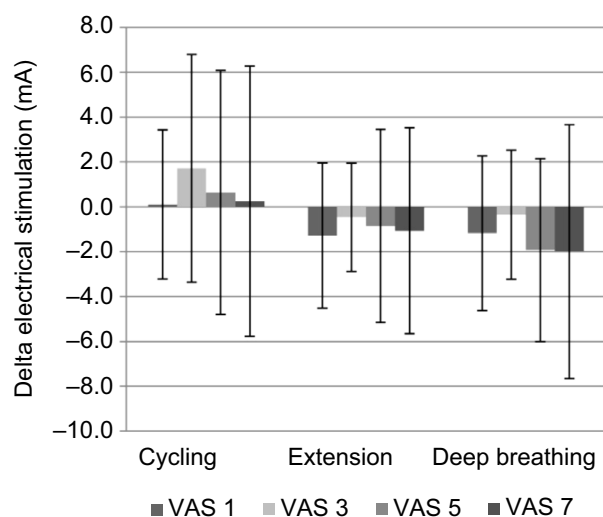


**Table 2** Outcomes of the pain measurement at baseline and after aerobic cycling exercise, isometric knee extension and the control condition

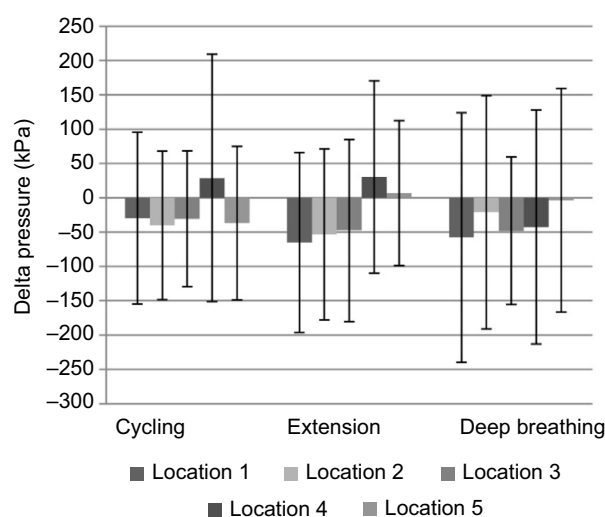
Pain test	Baseline, mean (SD)	Aerobic cycling, mean (SD)	Isometric extension, mean (SD)	Control condition, mean (SD)
<b>Visceral stimulation (mA)</b>				
VAS 1	9.1 (3.6)	9.2 (4.6)	7.8 (2.9)	7.9 (4.6)
VAS 3	11.7 (3.4)	13.4 (6.5)	11.3 (3.5)	11.4 (4.6)
VAS 5	17.9 (7.1)	18.6 (8.2)	17.1 (6.0)	16.0 (5.2)
VAS 7	22.0 (8.4)	22.2 (8.7)	20.8 (7.2)	19.8 (4.8)
<b>Pressure algometry (kPa)</b>				
Trapezius muscle	491 (118)	461 (143)	426 (111)	433 (184)
T10 dermatome	549 (142)	509 (124)	496 (114)	528 (145)
Thenar muscle	493 (116)	462 (77)	445 (85)	445 (100)
Rectus femoris muscle	641 (179)	669 (154)	671 (185)	598 (134)
Adductor hallucis muscle	552 (141)	515 (98)	559 (115)	548 (157)
<b>CPM</b>				
PPT before (kPa)	677 (148)	688 (161)	679 (137)	619 (139)
PPT after (kPa)	724 (154)	756 (198)	777 (145)	775 (227)
VAS 30 seconds	4.6 (1.7)	4.9 (2.4)	5.1 (2.1)	5.2 (1.9)
VAS 60 seconds	6.5 (1.6)	6.3 (2.1)	6.4 (1.6)	6.8 (1.5)
VAS 90 seconds	7.5 (1.4)	7.1 (1.5)	7.4 (1.4)	7.5 (1.3)
VAS 120 seconds	7.9 (1.2)	7.7 (1.4)	8.0 (1.3)	8.1 (1.2)
VAS overall	6.9 (1.2)	6.9 (1.6)	7.1 (1.5)	7.3 (1.4)

**Notes:** PPT before: pressure pain threshold before cold pressor test, PPT after: pressure pain threshold after cold pressor test and VAS overall: mean VAS scores during the immersion.

**Abbreviations:** SD, standard deviation; VAS, visual analogue scale; CPM, conditioned pain modulation.

**Figure 3** Visceral stimulation.

**Note:** Baseline-corrected mean intensities (mA) where participants rated 1, 3, 5 and 7 on the visual analogue scale (VAS) after aerobic cycling, isometric knee extension and the control condition.

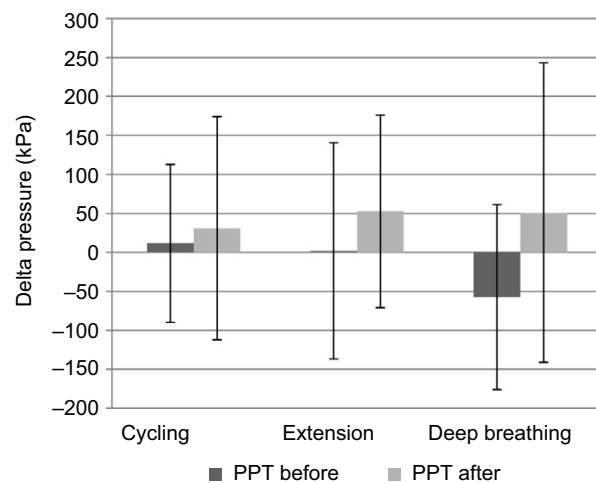
**Figure 4** Pressure algometry.

**Note:** Baseline-corrected mean pressure pain thresholds at the trapezius muscle (location 1), T10 dermatome (location 2), thenar muscle (location 3), rectus femoris muscle (location 4) and adductor hallucis muscle (location 5) after aerobic cycling, isometric knee extension and the control condition.

## CPM

Except for one, all participants were able to complete the 2-minute cold pressor tests. An overall increase in PPTs was found after CPM induction ( $F(1, 42)=14.8$ ;  $p=0.002$ ; Figure 5). The mean (SD) relative increase for baseline was 9.3% (20.1), for aerobic cycling 10.2% (15.4), for isometric knee extension 16.1% (15.9) and for deep breathing 25.5% (22.5). However, no significant difference in CPM effect

was found between the conditions ( $F(2, 28)=2.9$ ;  $p=0.07$ ). The effect size for the aerobic cycling was  $d=0.81$  and for isometric exercise  $d=0.49$ . No significant differences were found between mean VAS scores during the cold pressor test, which were 6.7 (1.8) at baseline, 6.6 (2.1) after aerobic cycling, 6.8 (1.9) after isometric extension and 7.0 (1.8) after deep breathing ( $F=1.0$ ;  $p=0.4$ ).



**Figure 5** Conditioned pain modulation.

**Note:** Baseline-corrected pressure pain thresholds (PPT) before and after the cold pressor test after aerobic cycling, isometric extension and the control condition.

**Table 3** Heart rate (HR) during aerobic cycling, isometric extension and the control condition

HR	Aerobic cycling, mean (SD)	Isometric extension, mean (SD)	Control condition, mean (SD)
Rest <sup>a</sup>	63 (7.2)	76 (13.4)	69 (7.9)
End <sup>b</sup>	162* (9.6)	86 (11.3)	64 (7.6)
Mean <sup>c</sup>	164* (5.7)	87 (11.4)	66 (7.6)

**Notes:** <sup>a</sup>HR rest was measured before the interventions. <sup>b</sup>HR end was measured at the end of aerobic cycling and isometric knee extension. In the control condition, "HR end" was the minimum HR in every round of deep breathing. <sup>c</sup>HR mean was the mean heart rate over the complete intervention. \*Significant increase;  $p < 0.001$ .

## Cardiovascular responses and exertion during interventions

Data are presented in Table 3.

### Aerobic cycling exercise

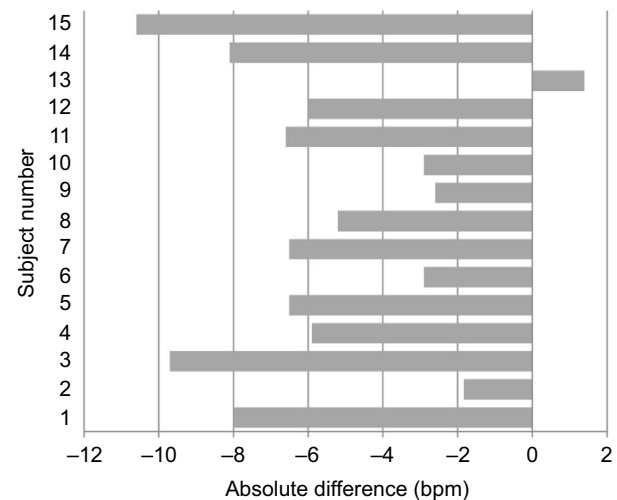
The mean HR of the participants during the 20 minutes of cycling ranged between the target intensities 75% to 88%. There was a significant increase from HR during rest to HR during exercise ( $F(2, 42)=801$ ;  $p < 0.001$ ). Borg scores increased significantly (from 6 (0.5) to 16 (2.2);  $F(2, 42)=175$ ;  $p < 0.001$ ).

### Isometric knee extension

There was no significant increase in HR during isometric knee extension. However, Borg scores increased significantly (from 6 (0.7) to 15 (1.6);  $F(2, 42)=137$ ;  $p < 0.001$ ).

### Control condition

Figure 6 shows the mean absolute difference between the starting HR and the lowest HR in every round of deep



**Figure 6** Heart rate during deep breathing.

**Notes:** Mean absolute difference between start heart rate (HR) and minimum HR in every round of deep breathing in the control condition. Data are presented for each participant individually.

**Abbreviation:** bpm, beats per minute.

breathing for every individual. Except for one participant, HR decreased, with a mean (SD) of 5.4 beats per minute (4.9). However, no significant decrease was found when comparing the mean values of all participants.

## Discussion

The aim of this study was to evaluate the effect of different exercise modalities on visceral and somatic pain sensitivity and CPM, compared to deep breathing as active control condition. Unexpectedly, no significant effects of aerobic and isometric exercise were found on any of the pain tests. Furthermore, no differences between the exercise conditions and control condition were found. These results suggest that exercise may not change pain evoked in healthy subjects.

Our findings contradict other studies, which found higher PPTs during and after exercise, using similar types of aerobic and isometric exercise.<sup>2,3,6,9</sup> However, this effect was not consistently found, likely due to many methodological variations and the absence of a control condition in many previous studies. Another difference when comparing the literature is that our study was performed on 1 day to maintain similar physiological and emotional states. To minimize period and carry over effects, the interventions were randomized and a 30-minute washout period was held between the end of pain measurements and the beginning of the next intervention. The number of participants included in the study is comparable to previous studies with similar exercise interventions; however, insufficient reliable input assumptions were available to perform a prospective power analysis. The relative small



sample size and low statistical power could have influenced the nonsignificant results.

In this study, deep breathing was used as active control condition, compared to no control condition or quiet rest in previous studies.<sup>2,3,10</sup> Positive characteristics of deep breathing are the control for increased breathing intensity, which occurs also during exercise, without the physical exercise and increase in HR. Furthermore, distraction during the interventions is taken into account, as participants are supposed to focus on their breathing. However, 2 main concerns have to be considered for the use of deep breathing as active control condition. First, the response to deep breathing differs among individuals and it is difficult to objectively measure the largely unknown variations in this response. Second, the deep breathing could have induced a hypoalgesic effect of itself, which makes the interpretation of the study effects complicated. It has been shown that slow, deep breathing results in lower heat pain intensity ratings<sup>36</sup> and increased thermal pain thresholds,<sup>37</sup> induces hypoalgesia for suprathreshold electrical stimulations<sup>38</sup> and prevents the development of acid-induced esophageal hypersensitivity.<sup>35</sup> It is thought that HR variability and thus parasympathetic activity during deep breathing might contribute to the hypoalgesic effect by shared cardiorespiratory and nociceptive neurophysiological pathways,<sup>35,37</sup> although this is not consistently found.<sup>38</sup>

Various parameters for determining exercise intensities at which hypoalgesia would occur have been investigated in healthy individuals. Naugle et al<sup>9</sup> showed a dose-response effect between cycling exercise intensity and hypoalgesic effect. According to American College of Sports Medicine, intensities corresponding to 60% to 80% of the  $\text{VO}_{2\text{max}}$  are favorable for developing cardiovascular fitness and thus often used for training. Corresponding to this intensity, Swain et al<sup>39</sup> recommended the use of 75%–88% of HR maximum, which is a more practical method of measuring the intensity. Therefore, in our study, HR was used to monitor the exercise intensity, using the Karvonen formula to calculate the individual target HR, which takes the resting HR and age-related maximum HR into account.<sup>9</sup> However, this monitored intensity could only be used for the aerobic exercise and not for isometric exercise, which makes it impossible to compare the physiological stress between the exercise conditions.

During isometric exercise, the strongest effect of hypoalgesia has been shown at low-to-moderate intensity held for longer durations, as high-threshold motor units become increasingly activated to maintain the required force. Consequently, a plausible explanation is that in order to evoke hypoalgesia, high-threshold motor units need to be

recruited.<sup>1,8</sup> Synergistically, central inhibitory pathways might be activated, as studies showed an extrasegmental hypoalgesic effect, thus not restricted to the contracting muscle. In the same line, the hypoalgesic effect on heterotopic body parts was shown to be comparable to that on the contracting muscle.<sup>1</sup> Our nonsignificant results could not reproduce these previous findings. The isometric knee extension was performed for 12 minutes with a 0.75 kg weight attached around the ankle.<sup>6</sup> This produced the same strenuous intensity for every participant and therefore this was preferred over other methods, in which a dynamometer is used to assess the maximal voluntary contraction.

In this research, 2 different exercise types were used to evaluate different cardiovascular responses. An inverse relationship between resting BP and pain perception has been found,<sup>40</sup> and a few studies investigated the interaction between exercise, BP and hypoalgesia. There is some evidence for the hypothesis that an interaction exists between pain modulatory and cardiovascular systems, involving the same neuropeptides (e.g., opioids), neurotransmitters (e.g., monoamines) and brain stem nuclei (e.g., nucleus tractus solitarius and locus coeruleus).<sup>1,20,40–42</sup> The HR increased significantly during aerobic cycling and not during isometric extensions, thus the cardiovascular responses was dissimilar. However, no differences between the hypoalgesic effects were found.

An acute experimental pain model was used to induce visceral pain in healthy volunteers. In patients, pain is a subjective experience, influenced by many factors, for example, emotional and psychological aspects, genetics and cultural background. This makes it difficult to characterize pain mechanisms and hypoalgesic effects. The use of an experimental pain model prevents some of this bias and facilitates a controlled frequency, duration, intensity and localization of the pain stimuli. To mimic the clinical setting as much as possible, different pain modalities can be used, such as mechanical, thermal, electrical and chemical stimuli, and the pain perception can be assessed both subjectively (using the VAS) and objectively (e.g., with nociceptive reflexes or cerebral evoked potentials).<sup>43</sup> With these characteristics, experimental pain models help reduce the gap between pre-clinical studies and clinical trials.

There are some limitations inherent in this study. First, only electrical stimulations were used to induce visceral pain in the experimental pain model, due to ethical and practical motives. Electricity stimulates afferent nerves directly, therefore bypassing receptors. Furthermore, the 4-hour long position of the esophageal probe during exercise was not

visually controlled, as endoscopy was avoided to minimize the unpleasantness. Even though impedance was controlled before stimulation, it was not checked after the interventions, and hence this may affect pain measurements. As innervation and nerve density of the esophagus are unevenly distributed, minor changes in probe position could in themselves lead to differences.<sup>44</sup> It is challenging to measure visceral pain sensitivity objectively as it is difficult to characterize for both patients and investigators. However, it remains important to study this pain type, as it is a common cause of chronic pain with limited treatment possibilities.<sup>45</sup>

## Conclusion

This explorative study was the first to investigate the effect of aerobic and isometric exercise on visceral and somatic pain in an experimental pain model, compared to deep breathing as an active control condition. No significant differences were found for the psychophysical tests after the 2 exercise interventions compared to the control condition, although methodological problems cannot be excluded. The hypoalgesic effect of exercise appears to be less stable than initially thought. Further studies are recommended to increase our knowledge about the effect of exercise and deep breathing on pain perception, including comparisons of the effect of exercise on different types of pain between exercise interventions and an equivalent control condition.

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## Disclosure

The authors report no conflicts of interest in this work.

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